UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte PETER M. GLAZER and PAMELA A. HAVRE

Appeal No. 2005-0733
Application No. 09/783,338[1]

HEARD: July 14, 2005

Before SCHEINER, ADAMS and MILLS, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 6-14 (the only claims remaining in the application) under the first paragraph of 35 U.S.C. § 112. There is no dispute that "the central issue on Appeal is whether the claims, as they relate to [an] in vivo [method], lack enablement." Reply Brief, page 1.

The present application is a continuation of U.S.S.N. 08/083,088.[2] The claims in the parent application were much the same as the claims in the present application (see the comparison below), and were rejected on the same basis. Following an appeal of the rejection in that case (Appeal No. 1997-2520, opinion dated February 28, 2001), the board agreed that the examiner had established a reasonable basis for questioning the enablement of the claims, and affirmed the examiner's rejection.

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[1] Application for patent filed February 14, 2001.

[2] Application for patent filed June 23, 1993, now abandoned.

According to appellants, "[e]vidence showing in vivo as well as additional evidence of in vitro efficacy was obtained after filing of the appeal [in the parent case], but could not be considered in [that] appeal. The present application was filed so that such evidence could be considered (submitted in the form of a Declaration under [37 CFR § 1.132])." Brief, page 2.

THE CLAIMED SUBJECT MATTER

Claim 6 is representative of the subject matter on appeal and reads as follows:

6. A method for site-directed mutagenesis of a nucleic-acid molecule comprising the steps of:

a) hybridizing a mutagenic oligonucleotide to a target region of a double-stranded nucleic acid molecule, wherein the mutagenic oligonucleotide comprises a mutagen incorporated into a single-stranded nucleic acid that forms a triple-stranded nucleic acid molecule with the target region; and

b) mutating the double-stranded nucleic acid molecule.

The corresponding claim in U.S.S.N. 08/083,088 is as follows (differences emphasized):

6. A method for site-directed mutagenesis of a nucleic acid molecule **consisting of** steps of:

a) hybridizing a mutagenic oligonucleotide to a target region of a double-stranded nucleic acid molecule **in a cell**, wherein the mutagenic oligonucleotide comprises a mutagen incorporated into a single-stranded nucleic acid that forms a triple-stranded nucleic acid molecule with the target region; and

b) mutating the double-stranded nucleic acid molecule.

DISCUSSION

In deciding the appeal in U.S.S.N. 08/083,088 (Appeal No. 1997-2520), the parent of the present application, the board considered the examiner's thorough analysis of appellants' disclosure under the so-called Wands factors,[3] and concluded that "the totality of the evidence presented by the examiner and appellants weigh[ed] in favor of finding lack of enablement of the claimed invention" (page 13 of the opinion in Appeal No. 1997-2520). In the present case, however, appellants have submitted "[e]vidence of reduction to practice in intact animals . . . in the form of a Declaration . . . to prove the truth of the statements in the application" (Brief, page 7). As the examiner explains, "the Declaration by Dr. Glazer[4] . . . represents the only new evidence in this application" (Answer, page 10), so we will focus our discussion on whether or not the Declaration is adequate to address the examiner's concerns and to rebut the examiner's rejection.

In a nutshell, the examiner's concerns with respect to the in vivo aspects of the claimed invention involve "issues of [oligonucleotide] delivery, penetration," and "triplex formation" (Answer, page 7) in an intact animal. The examiner acknowledges that "[t]he specification [demonstrates] site specific, targeted mutagenesis . . . in an in vitro method" and "in an ex vivo type method" (id., page 5), but argues that "there is no

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[3] Factors to be considered in determining whether a disclosure is unenabling because it would require undue experimentation to practice the invention have been summarized by the board in Ex parte Forman [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims (footnote omitted).

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

[4] Submitted December 3, 2002.

correlation between the entry of the oligonucleotide-mutagen complex in isolated cells in an ex vivo method and in vivo applications where entry into an animal is required" (id.), largely because "the precise role of nucleases, other intracellular enzymes and proteins on the stability of [ ] ribozymes, . . . [mechanisms] by which oligonucleotides penetrate cellular membranes and distribute in cells, [ ] non-sequence-specific interactions[,] . . . metabolism of antisense drugs . . . and cellular parameters such as cell type, cell cycle phase and differentiation stage" (id., page 6) are poorly understood and unpredictable.

In his declaration, Dr. Glazer describes the protocols and results of experiments in which mice were given intraperitoneal injections of a triplex-forming oligonucleotide (TFO) designed to bind to a predetermined site on the *supFG1* gene. See section 12, pages 6-14 of the Declaration. The examiner does not dispute Dr. Glazer's assertion that the mouse experiments described in the Declaration "demonstrate that site-specific, TFO-directed genome modification can be accomplished in intact animals" (Declaration, page 7). Rather, the examiner argues that the in vivo experiments described in the Declaration are not commensurate in scope with the claimed invention because the mutagenic oligonucleotide used in the mouse experiments differs from the oligonucleotide used in the specification's in vitro and ex vivo examples in that it does not have a discrete mutagen associated with it. See pages 11 and 12 of the Answer.

As explained by Dr. Glazer, however, in vitro experiments established that targeted mutagenesis was seen with and without psoralen[5] conjugation, "suggesting a substantial triplex-mediated process of mutagenesis" (Declaration, page 7), and appellants argue that "there has been no evidence provided by the examiner that the

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[5] Psoralen is a known mutagen.

in vivo evidence in the Declaration would not be predictive of an oligonucleotide which further included a small molecule mutagen such as a psoralen" (Reply Brief, page 5). In any case, it does not appear that the examiner has questioned the ability of an attached mutagen to cause a mutation in a double-stranded nucleic acid molecule, once delivered to a cell.

In our opinion, the examiner has not explained why the mouse experiments described by Dr. Glazer are not relevant to the examiner's stated concerns: "issues of [oligonucleotide] delivery, penetration," and "triplex formation" (Answer, page 7). On this record we see no reason to dispute appellants' assertion that the experiments described in the Declaration demonstrate "the ability of the oligonucleotide to specifically bind the target gene[;] formation of a stable complex between the oligonucleotide and the target gene[;] uptake of the oligonucleotide by the cell[;] and [ ] solubility of the nucleotide in the cell" (Brief, page 12).

Finally, we note the examiner's assertion that "simply correcting a few cells of [an] arbitrary mutation created in the mouse is not enough for a patentable use" "since no therapeutic effect has been shown for any of the oligonucleotides" (Answer, page 11) and in any case, "[t]he mutations must be corrected in sufficient amounts to yield some benefit or there is no patentable use for the correction method" (id., pages 11-12). Nevertheless, the claims have not been rejected as lacking utility, and we perceive no requirement in the claims that the method have any therapeutic effect.

In our view, the Declaration of Dr. Glazer provides evidence sufficient to rebut the examiner's initial basis for questioning the enablement of the claimed invention. Accordingly, the rejection of claims 6-14 under the first paragraph of 35 U.S.C. § 112 is reversed.

REVERSED

Toni R. Scheiner
Administrative Patent Judge

Donald E. Adams
Administrative Patent Judge

Demetra J. Mills
Administrative Patent Judge

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